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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,902	11/17/2000	John James Donnelly	1627.003	5612

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/715,902	Applicant(s) Donnelly
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 14, 2003*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above, claim(s) *24-28* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-23 and 29-53* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 12
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's response received on 1/14/03 has been entered. New claims 32-53 have been added. Claims 1-53 are pending in the instant application. This application contains claims 24-28 drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Claims 1-23 and 29-53 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action, can be found in previous office actions.

Priority

The applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: provisional US Application No. 60/146,391, filed on 7/29/99, was filed more than 12 months prior to the filing of the instant application. The applicant is not entitled to claim benefit of priority to a provisional application filed more than 12 months before the filing of the instant application. As a result, the office does not acknowledge priority to 60/146,391. However, the office does acknowledge applicant benefit of priority to

provisional US Application No. 60/166,514, which was filed on 11/19/99. For the record, the effective priority date of the instant application is considered to be the filing date of the 60/166,514 application, which is 11/19/99.

Claim Rejections - 35 USC § 103

The rejection of claims 1-23 and 29-31 under 35 U.S.C. 103(a) as being unpatentable over WO 97/24447, 7/10/97, hereafter referred to as Song et al., in view of US Patent No. 5,783,567 (7/21/98), hereafter referred to as Hedley et al., and further in view of Fattal et al. (1998) J. Controlled Rel., Vol. 53, 137-143, is maintained and extended to include applicant's new claims 32-53. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant argues that the prior art cited by the office does not provide sufficient motivation or a reasonable expectation of success for making /using applicant's claimed invention, citing MPEP 2143 and *In re Mills* . In response, it is noted that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific

references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Furthermore, it is well-established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). In the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Most importantly, obviousness does **not** require absolute predictability of success; for obviousness under 35 U.S.C. 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

In response to applicant's arguments concerning each reference individually, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant's arguments regarding the teachings of each reference are addressed below in the context of the combined teachings of Song et al., Hedley et al., and Fattal et al.

The applicant acknowledges that Song et al. teaches several gene delivery vehicles for gene livery to dendritic cells, but argues that Song et al. does not teach a transfection agent comprising a polynucleotide and a microparticle as claimed. The applicant further argues that neither Hedley et al. nor Fattal et al. overcome this deficiency in Song. As discussed in detail in the previous office action, Song et al. teaches methods of transfecting dendritic cells *ex vivo* or *in vitro* with a gene delivery vehicle comprising DNA encoding an antigen such as a tumor antigen

or HIV antigen, and use of said transfected dendritic cells to induce an immune response against the expressed antigen in vivo (Song et al., pages 2, 3, and 18-20). Regarding new claims limitations to fungal, bacteria, and parasitic antigens, Song et al. teaches the use of antigens from bacteria, fungi, parasites, and viruses (Song et al. pages 20, lines 1-7). Song et al. also teaches that the transfected dendritic cells can be administered to a vertebrate parenterally or by direct injection, and that the dendritic cells can be derived from bone marrow and cultured for at least 7 days prior to transfection (Song et al., pages 26 and 39). Song et al. also teaches wherein the DNA encoding an antigen is a plasmid DNA (Song et al., page 18). Delivery vehicles taught by Song et al. include expression vectors complexed with polycations or lipids or encapsulated in liposomes. Song teaches that for *ex vivo/in vitro* transfection of dendritic cells, both non-viral and viral gene delivery vehicles can be used (Song et al., page 1, and pages 14-19). Thus, Song et al. teaches that numerous gene delivery vehicles can be successfully utilized to transfect dendritic cells including the use of plasmid/liposomes, and plasmid combined with cationic condensing agents.

Hedley et al. supplements Song et al. by teaching the use of microspheres comprising biodegradable polymers and DNA plasmids to introduce and express antigens encoded by the plasmids in antigen presenting cells such as macrophages and dendritic cells both *in vitro* and *in vivo* for the purpose of stimulating antigen specific immune responses (Hedley et al., columns 2-3 and 7-8). Hedley et al. further teaches that numerous biodegradable polymers and copolymers can be used to form the microspheres including poly(lactide) and poly (caprolactone) (Hedley et al.,

columns 10-11). As a preferred embodiment, Hedley et al. teaches the use of the copolymer (D, L-lactide-co-glycolide) (Hedley et al., column 11). Hedley et al. further teaches the preparation of microparticles comprising plasmid DNA which have a size of about 1 micron (Hedley et al., column 14). Hedley et al. further provides motivation for introducing plasmid DNA encoding an antigen to dendritic cells and macrophages by teaching that DNA combined with biodegradable microparticles is efficiently phagocytosed by APCs and is an effective means for introducing nucleic acids into these cells (Hedley et al., column 8, lines 13-49).

The applicant argues that Hedley et al. does not provide motivation for using microparticles to transfect dendritic cells and that the techniques disclosed by Hedley et al. are *in vivo* techniques. In response, Hedley teaches both *in vitro* and *in vivo* transfection of cells, see in particular column 15. The fact that Hedley exemplifies *in vitro* transfection with macrophages does not teach away from the essential teachings of Hedley et al. that biodegradable microparticles comprising plasmid DNA can be used to transfect antigen presenting cells including dendritic cells. Specifically, Hedley et al. teaches that phagocytosis of microparticles by macrophages and other antigen presenting cells is an effective means for introducing the nucleic acid into these cells (Hedley et al., column 8, lines 13-15). At the time of filing, dendritic cells were known to by capable of phagocytosis. Hedley et al. also specifically identifies dendritic cells as targets for microparticle transfection (Hedley et al., column 8, lines 25-27). Furthermore, the applicant is reminded that Hedley has been cited to supplement the teachings of Song et al., which specifically teach *ex vivo* gene delivery to dendritic cells. Motivation for *ex vivo* transfection of

dendritic cells is provided by Song et al. Hedley et al. provides motivation for transfecting phagocytic cells such as dendritic cells using biodegradable microparticles. As stated in the previous office action, based on the motivation to introduce nucleic acids into macrophages and dendritic cells using biodegradable polymers as taught by Hedley et al., it would have been *prima facie* obvious to the skilled artisan to use biodegradable particles and plasmid DNA as the gene delivery vehicle in the methods of transfecting dendritic cells and methods of immunizing taught by Song et al. Further, based on the efficiency of phagocytosis of biodegradable particles taught by Hedley et al., the skilled artisan would have had a reasonable expectation of success in using biodegradable particles to deliver polynucleotides to phagocytic dendritic cells *in vitro*.

In regards to the teachings of Fattal et al., the applicant argues that increased uptake of nucleic acid is due to association with nanoparticles rather than by increased uptake of nanoparticles by phagocytosis. In response, Fattal et al. teaches that the association of oligonucleotides with particles comprised of biodegradable polymers is increased by the addition of cationic detergents such as CTAB (Fattal et al., pages 137 and 139, Figure 1). Fattal et al. further reports efficient phagocytosis/endocytosis of nanoparticles made using a cationic detergent (Fattal et al., page 137). Thus, Fattal et al. provides motivation for including a cationic detergent such as CTAB in the preparation of transfection agents comprising biodegradable polymers and polynucleotides in order to increase the amount of polynucleotide associated with the polymer particles and increase the uptake of the nucleic acid by phagocytosis. In view of the motivation provided by Fattal et al. discussed above, it would have been *prima facie* obvious to

the skilled artisan at the time of filing to include a cationic detergent in gene delivery vehicle comprising biodegradable polymers in order to increase the association of polynucleotide with the particle and thus to increase phagocytosis of the nucleic acid by the target cell. Further, the skilled artisan would have had a reasonable expectation of making and using a transfection agent comprising a polynucleotide and biodegradable polymer particles comprising a cationic detergent to transfect dendritic cells based on the successful use of oligonucleotide nanoparticles comprising biodegradable polymer and CTAB taught by Fattal et al. to transfect cells *in vitro* and *in vivo*.

In regards to applicant's comments regarding the absorption versus the entrapment of nucleic acids by the microparticles, applicant's claim encompass both situations, see in particular the limitations of new claims 45-51. Hedley et al. and Fattal et al. provide evidence that nucleic acids can be efficiently delivered to phagocytic cells when they are either absorbed onto biodegradable particles, see Fattal et al., or entrapped with biodegradable microparticles, see Hedley et al. Thus, the teachings of Fattal et al. and Hedley et al. are not in conflict. The ultimate goal is gene delivery to a cell capable of phagocytosis. In view of the teachings of Fattal et al. and Hedley et al., the skilled artisan would be equally motivated to absorb or entrap nucleic acids to biodegradable particles in order to transfect phagocytic cells, and in particular dendritic cells according to the teachings of Song et al.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER